J Life Sci Res 2014; **12**: 3-7

Journal of Life Science Research
Online ISSN 2186-5809

Review

What to eat first and how to eat to reduce amplitude of glycemic excursions

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Received 10 August 2014; accepted 20 September 2014

Key words : diabetes; diet; CGM; glycemic excursions

1 Introduction

Large glucose excursions are reported to promote the macro-vascular complications associated with type 2 diabetes (T2D).[1–3] Postprandial hyperglycemia and glycemic spikes are more strongly associated with atherosclerosis than fasting plasma glucose or HbA1c level.[4] Hyperglycemia is associated with increased risk for atherosclerosis by suppressing endothelium-dependent vasodilation, activating thrombosis, and increasing oxidative stress in people with T2D,[5, 6] with impaired glucose tolerance (IGT), [7] and even in subjects with normal glucose tolerance (NGT).[8] A reduction in postprandial hyperglycemia by an α-glucosidase inhibitor delayed progression of carotid intima-media thickening in subjects with T2D.[9]

A significant number of patients with diabetes remain poorly controlled, mainly as a result of poor diet compliance.[10–12] Patients with diabetes are advised to adopt an appropriate diet to affect blood glucose control by patients themselves, not by their physicians or other medical professionals on a lifelong basis. Traditionally, diets of T2D aim to restrict energy intake and provide macronutrient balance. However, some diabetic patients may have difficulty understanding diets based on a restrict energy intake, as well as changing their daily food habits. Therefore, easy and effective diets are needed to reduce glycemic fluctuations and minimize hypoglycemic events in addition to improving mean blood glucose.

In this article we reviewed our recent studies about the effects of consuming "vegetables before carbohydrates" on the reduction in glucose fluctuations.

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2 Evaluation of efficacy of consuming vegetables before carbohydrates on glucose excursions

A continuous glucose monitoring system (CGMS) is capable of detecting hypoglycemia and hyperglycemia that may be undetectable by self-monitoring blood glucose and HbA1c.[13] Particularly, the mean amplitude of glycemic excursions (MAGE) is a significant determinant of overall metabolic control, as well as increased risk of diabetes complications.[1–3, 14] We examined whether consuming vegetables before carbohydrates could reduce the daily postprandial glucose excursions assessed by CGMS in Japanese patients with T2D and subjects with NGT.

All participants were assigned to CGMS (Medtronic Minimed Gold, Northridge, CA) for 72-h by consuming test meals of vegetables before carbohydrates and carbohydrates

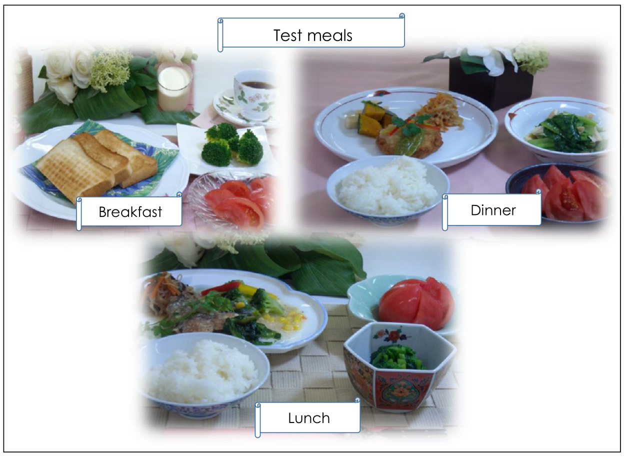

Fig. 1 The test meals of the study. The subjects ate the first dishes of vegetables for 5 min, then the main dish for 5 min, and consumed rice or bread for 5 min successively within a 15 to 20 min total eating time for each meal, and *vice versa*.

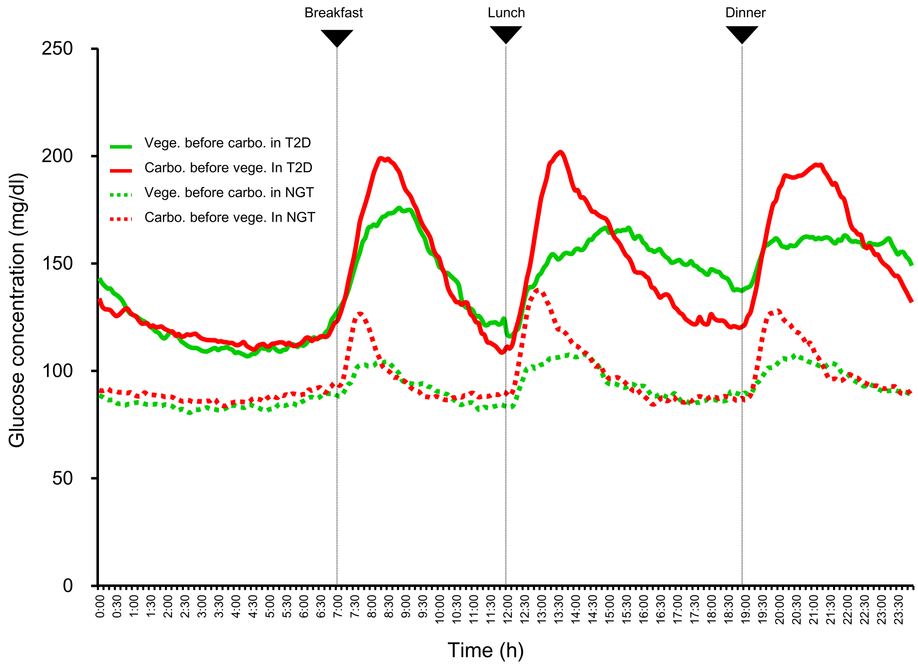

Fig. 2 The mean of the daily glucose values was plotted to show the reduction in glucose excursions by consuming vegetables before carbohydrates compared to the reverse regimen in both subjects with type 2 diabetes (T2D, n = 19) and normal glucose tolerance (NGT, n = 21).

before vegetables on the 2^{nd} and the 3^{rd} day in a randomized crossover design. The test meals consisted of rice/bread, meat/fish, 500 g of vegetables (tomato, spinach, broccoli, and radish, etc), and contained 21 g of dietary fiber and 125.6 kJ kg^{-1} per day. The energy ratio of protein, fat, and carbohydrates was 17%, 25%, and 58%, respectively. The subjects ate the first dishes of vegetables for 5 min, then the main dish for 5 min, and consumed rice or bread for 5 min successively within a 15 to 20 min total eating time for each meal, and *vice versa* (Fig. 1).

Nineteen outpatients with T2D (male/female; 6/13, age; 65.5 ± 9.4 yrs, duration of diabetes; 16.4 ± 10.2 yrs , BMI; 22.5 ± 3.1 kg/m^2, HbA1c; 7.2 ± 1.0%, FPG; 145 ± 48 mg/dl, diet/oral hypoglycemic agents/insulin treatment; 3/3/13: mean ± SD or *n*) and 21 subjects with NGT (male/female; 2/19, age; 29.8 ± 11.3 yrs, BMI; 20.8 ± 3.0 kg/m^2, HbA1c; 5.4 ± 0.6%, FPG; 88 ± 9 mg/dl) were enrolled in the study. Glycemic parameters between the day of consuming vegetables before carbohydrates and the day of consuming carbohydrates before vegetables were examined.

The mean of the daily glucose values was plotted to show the reduction in glucose excursions of consuming vegetables before carbohydrates compared to the reverse regimen in subjects with T2D and NGT (Fig. 2).[15] The levels of standard deviation, MAGE, large amplitude of glycemic excursions, mean 1-h postprandial glucose, mean incremental area under the glucose curve 0-3h, and mean incremental glucose peak were all significantly reduced when the participants ate vegetables before carbohydrates compared to the reverse regimen in both subjects with T2D and NGT.[16]

3 The effect of consuming vegetables before carbohydrates on postprandial glucose and insulin

We reviewed the effect of eating vegetables before carbohydrates on postprandial plasma glucose and insulin in patients with T2D. We conducted a randomized crossover study in 15 outpatients with T2D controlled by diet (male/female; 7/8, age; 61.7 ± 11.6 yrs, duration of diabetes; 5.3 ± 8.8 yrs , BMI; 24.7 ± 4.3 kg/m^2, HbA1c; 6.4 ± 0.6%, FPG; 113 ± 20 mg/dl). Patients ate test meals consisting of 150 g white rice and vegetable salad (sliced tomato and cabbage with olive oil dressing), eating either vegetables before carbohydrates or *vice versa*. Plasma glucose and serum insulin levels were evaluated at 0, 30, 60, 120 min after consuming each test meal. Plasma glucose and serum insulin levels between consuming vegetables before carbohydrates and the reverse regimen were examined.

Postprandial plasma glucose levels in those following the vegetables before carbohydrates regimen were reduced at 30 and 60 min compared to the reverse regimen (217 to 172 mg/dl, $p < 0.01$, 208 to 186 mg/dl, respectively). Postprandial serum insulin decreased significantly about 30% at 30 and 60 min in the vegetables before carbohydrates regimen (32.9 to 22.3 µU/ml, $p < 0.01$, 35.4 to 24.9 µU/ml, p

< 0.05, respectively).[17]

4 The effect of consuming vegetables before carbohydrates on long-term glycemic control

In addition to lowering daily glycemic excursions, we studied whether educating diabetic patients to eat vegetables before carbohydrates was effective on long-term glycemic control. To test this hypothesis, we carried out a retrospective study in patients with T2D that compared changes in HbA1c as the primary outcome and changes in weight, serum lipids, and blood pressure as the secondary outcomes. A total of 333 outpatients were divided into two groups to receive instructions about consuming vegetables before carbohydrates (educational group, n = 196) or a control group (n = 137) who underwent a medical examination by a doctor. All patients were scheduled for return visits every 4 weeks with a physical examination and they were given general information about lifestyle and diabetes risk by either the doctor or nurses at every visit. The patients in the educational group were routinely scheduled to see registered dietitians at every visit. Depending on the patient's current dietary intake, intervention aimed to encourage increased consumption of vegetables, including seaweed and mushrooms, and consuming them first for 5 min, then the main dishes (meat, fish, soybeans etc.) for 5 min, and rice or bread, including potatoes, pumpkin, corn etc, successively within a 15 to 20 min eating time using an original educational brochure in the educational group (Fig. 3).

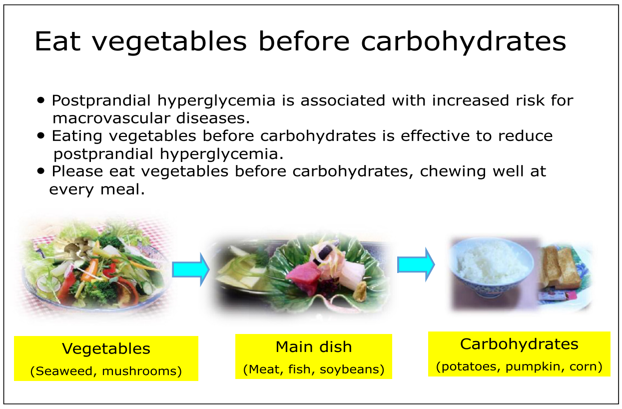

Fig. 3 The educational brochure about consuming vegetables before carbohydrates for the patients with type 2 diabetes.

Improvements in glycemic control were observed in patients in the educational group after the intervention and the levels of blood pressure, total cholesterol, and LDL cholesterol decreased significantly in both groups after 12 and 30 months (Table 1). After the intervention, dietary energy intake, protein, fat, and carbohydrates decreased in the educational group. These reductions in dietary nutrients were due to a decrease in the consumption of grain (rice), fruits, oil, sweets, and beverages, while the consumption of vegetables increased after intervention in the educational groups.[18]

5 What to eat first and how to eat to reduce amplitude of glucose excursions

This evidence supports the effectiveness of consuming vegetables before carbohydrates on daily glucose excursions and glycemic control in the long-term in patients with T2D. Dietary carbohydrates consumed after vegetables were digested slowly and required less insulin for subsequent metabolic disposal by the dietary fiber in the vegetables.[19–22] Other factors may influence the glycemic response and digestion of carbohydrates in the small intestine, including the rate of digestion, cooking method, transit time,

Table 1 Clinical parameters of patients in the two study groups

	Educational group (n = 196)			Control group (n = 137)		
	Baseline	1 y	2.5 y	Baseline	1 y	2.5 y
HbA1c (%)	8.6 ± 1.8	7.7 ± 1.8 ***†††	7.5 ± 1.7 ***†††	8.2 ± 1.5	8.3 ± 1.6	8.1 ± 1.7
BMI (kg/m^2)	24.2 ± 4.9	24.1 ± 5.3	22.9 ± 7.2 **	24.2 ± 4.0	24.4 ± 3.8	23.6 ± 5.3
SBP (mmHg)	132 ± 17	125 ± 11 ***†	127 ± 12 ***	138 ± 16	128 ± 12 ***	127 ± 10 ***
DBP (mmHg)	76 ± 11	72 ± 9 ***	71 ± 8 ***	75 ± 10	70 ± 8 ***	70 ± 8 ***†††
Total cholesterol (mg/dl)	215 ± 37	202 ± 36 ***	200 ± 36 ***	210 ± 34	201 ± 36 *	195 ± 38 ***
LDL cholesterol (mg/dl)	131 ± 33	121 ± 32 ***	117 ± 33 ***	124 ± 29	117 ± 26 *	113 ± 30 **
HDL cholesterol (mg/dl)	58 ± 16	59 ± 15	60 ± 17 *††	57 ± 14	57 ± 13	55 ± 14 *
Triglyceride (mg/dl)	142 ± 83	132 ± 76	127 ± 74 *	140 ± 89	153 ± 113	148 ± 117

Data are expressed as mean ± SD.

Baseline vs. 1 y or 2.5 y ; $^{*}p$ < 0.05, $^{**}p$ < 0.01, $^{***}p$ < 0.001

Educational group vs. Control group ; $^{\dagger}p$ < 0.05, $^{\dagger\dagger}p$ < 0.01, $^{\dagger\dagger\dagger}p$ < 0.001

BMI,body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Student's t tests were used to assess the difference between the clinical parameters in the two study groups and paired t tests were performed to analyze them within groups over time.

and the rate of intestinal absorption.[23–25] Horowitz et al. reported that whey protein and olive oil consumed before meals resulted in a substantial reduction in postprandial glycaemia in patients with diabetes.[26, 27] Protein and oil consumed before carbohydrates stimulate glucagon-like peptide 1 (GLP-1) secretion, and delay gastric emptying which leads to a reduction in glycemic excursions. However, in contrast to the reduced insulin secretion observed after eating vegetables, whey protein augmented insulin secretion, possibly by a combination of the incretin effect and the direct stimulation of β-cells by absorbed amino acids.[28] Effects of consuming vegetables before carbohydrates are probably similar to the gut peptide-based therapies for diabetes which may act predominantly by slowing gastric emptying when consuming oil and protein before the carbohydrates.

The approach of consuming vegetables before carbohydrates supports the concept of emphasizing food choices, what to eat first, how to eat, and not just to concentrate on energy intake. The most important point was that the method made it easy to make the appropriate behavioral changes, to increase the consumption of vegetables and to reduce the consumption of rice and sweets for patients with T2D. As one aspect of nutritional education, consuming vegetables before carbohydrates should be advised to patients with T2D and IGT,[29] and this advice could even be applicable to healthy people in order to prevent future cardiovascular events.

Acknowledgements

This study was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Science and Culture (23500809) and Osaka Prefecture University.

Conflict of Interest

The authors declare no potential conflicts of interest.

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